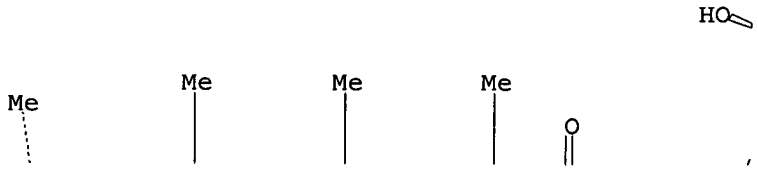
2/7/2005

ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN 476647-30-0 REGISTRY
ED Entered STN: 18 Dec 2002
CN Oxacycloheneicosa-3,5,7,11,13-pentaen-2-one, 10-[(6-deoxy-4-O-methyl-α-L-glucopyranosyl)oxy]-21-[O-2,6-dideoxy-3-O-methyl-β-D-arabino-hexopyranosyl-(1→4)-O-2,6-dideoxy-3-C-methyl-α-L-arabino-hexopyranosyl-(1→7)-2,4,6-trideoxy-1-C-hydroxy-2,4-dimethyl-8-O-methyl-L-glycero-β-D-galacto-octopyranosyl]-17,20-dihydroxy-18-methoxy-3,5,7,9,13-pentamethyl-, (3E,5E,7E,9R,10R,11E,13E,17S,18S,20S,21R)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN Isoapoptolidin
FS STEREOSEARCH
MF C58 H96 O21
SR CA
LC STN Files: BIOSIS, CA, CAPLUS, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
RL.NP Roles from non-patents: BIOL (Biological study); OCCU (Occurrence); PREP (Preparation); PRP (Properties)

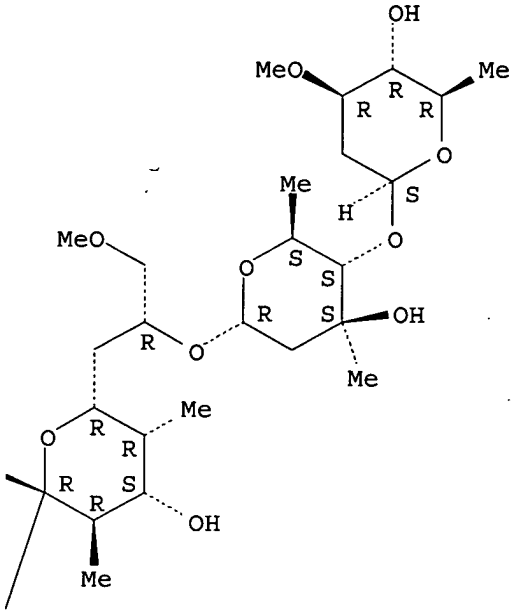
Ring System Data

Elemental Analysis EA	Elemental Sequence ES	Size of the Rings SZ	Ring System Formula RF	Ring Identifier RID	RID Occurrence Count
C5O	OC5	6	C5O	46.157.1	4
C2OO	OC2O	21	C2OO	7794.4.8	1

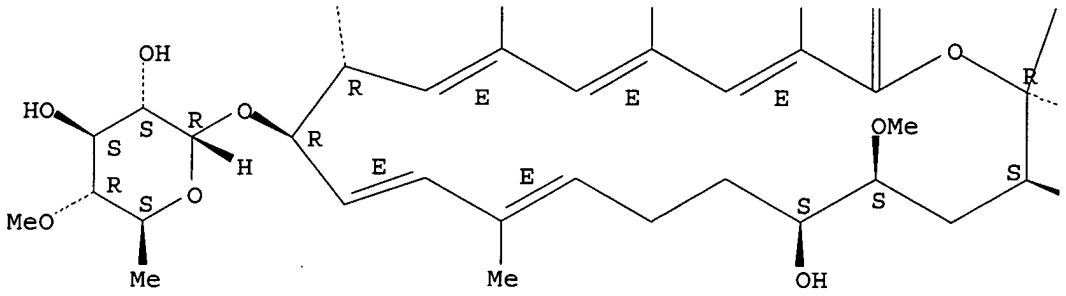
Absolute stereochemistry.
Double bond geometry as shown.



PAGE 1-B



PAGE 2-A



PAGE 2-B

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

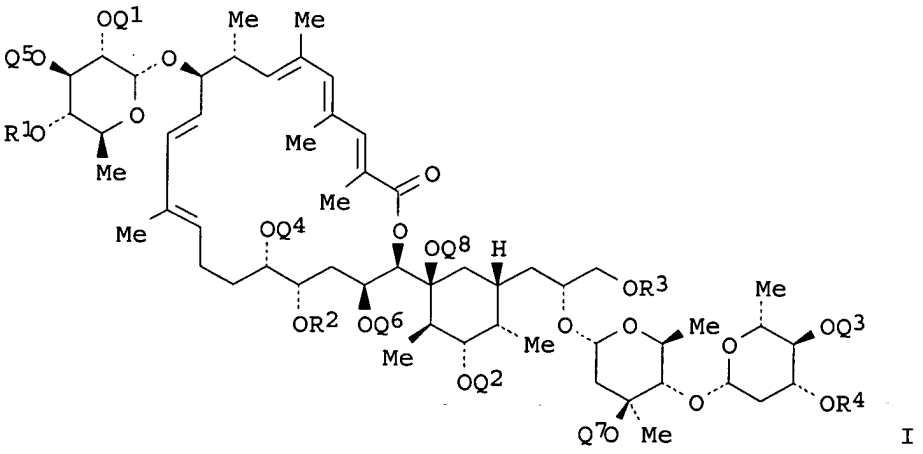
REFERENCE 1

ACCESSION NUMBER:	141:123857 CA
TITLE:	Preparation of apoptolidin analogs and derivatives for inducing apoptosis in transformed cells
INVENTOR(S):	Wender, Paul A.; Jankowski, Orion D.; Tabet, Elie A.
PATENT ASSIGNEE(S):	The Board of Trustees of the Leland Stanford Junior

University, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
INT. PATENT CLASSIF.:
MAIN: A61K
CLASSIFICATION: 33-4 (Carbohydrates)
Section cross-reference(s): 1, 7, 63
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004062629	A2	20040729	WO 2004-US935	20040113
WO 2004062629	A3	20041125		
W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ				
US 2004180841	A1	20040916	US 2004-757810	20040113
PRIORITY APPLN. INFO.:			US 2003-439954P	20030113
			US 2003-472657P	20030521

GRAPHIC IMAGE:



I

ABSTRACT:
The invention provides novel apoptosis-inducing compds. that include isolated, purified isoapoptolidin, and selectively functionalized isoapoptolidin derivs., wherein I (Q1-Q8 are independently selected from H, C1-C12 hydrocarbyl, acyl of the formula -(CO)-R5 in which R5 is C1-C12 hydrocarbyl, and hydroxy-protecting groups; and R1-R4 are C1-C12 alkyl or H) and stereoisomers thereof; selectively functionalized apoptolidin derivs. and stereoisomers thereof; and de-glycosylated isoapoptolidin and selectively functionalized derivs. and stereoisomers thereof. The isoapoptolidin, apoptolidin, and de-glycosylated isoapoptolidin derivs. may be functionalized by substituting any or all of the methoxyl or hydroxyl groups of the parent mol. Pharmaceutical compns. and methods for using the compds. are also provided. The invention also pertains to pharmaceutical compns. and methods for treating a patient in need of anticancer therapy or therapy for the treatment of other disorders that are

responsive to selective apoptosis, also known as programmed cell death.

SUPPL. TERM: enzyme inhibition oligosaccharide macrolide apoptolidin prepn apoptosis human prodrug; oligosaccharide macrolide apoptolidin analog prepn apoptosis isoapoptolidin human prodrug

INDEX TERM: Antitumor agents
Apoptosis
Chemotherapy
Human
Neoplasm
(preparation of antitumor apoptolidin analogs and derivs. for inducing apoptosis in transformed cells)

INDEX TERM: Oligosaccharides, preparation
ROLE: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antitumor apoptolidin analogs and derivs. for inducing apoptosis in transformed cells)

INDEX TERM: Drug delivery systems
(prodrugs; preparation of antitumor apoptolidin analogs and derivs. for inducing apoptosis in transformed cells)

INDEX TERM: 9000-83-3
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(F0F1; preparation of antitumor apoptolidin analogs and derivs. for inducing apoptosis in transformed cells)

INDEX TERM: 502156-06-1P 502156-08-3P 502156-13-0P 502156-19-6P
502156-20-9P 502156-21-0P 502156-22-1P 502156-23-2P
502156-25-4P 562106-87-0P 562106-88-1P 562106-89-2P
562106-92-7P 562106-93-8P 562106-94-9P
ROLE: IMF (Industrial manufacture); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antitumor apoptolidin analogs and derivs. for inducing apoptosis in transformed cells)

INDEX TERM: 194874-06-1, Apoptolidin 476647-30-0, Isoapoptolidin
ROLE: PAC (Pharmacological activity); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(preparation of antitumor apoptolidin analogs and derivs. for inducing apoptosis in transformed cells)

REFERENCE 2

ACCESSION NUMBER: 138:238351 CA
TITLE: Toward a Structure-Activity Relationship for Apoptolidin: Selective Functionalization of the Hydroxyl Group Array
AUTHOR(S): Wender, Paul A.; Jankowski, Orion D.; Tabet, Elie A.; Seto, Haruo
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305-5080, USA
SOURCE: Organic Letters (2003), 5(4), 487-490
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 33-3 (Carbohydrates)
Section cross-reference(s): 1

ABSTRACT:
To investigate the structural basis for the exceptional selectivity and

activity of apoptolidin, a strategy has been devised that allows for selective functionalization of seven of its eight hydroxyl groups based on progressive silyl protection, derivatization, and deprotection. The syntheses of these derivs. and their ability to inhibit F0F1-ATPase are reported.

SUPPL. TERM: regioselective acetylation silylation apoptolidin SAR ATPase inhibition; apoptolidin deriv prepn structure activity enzyme inhibition

INDEX TERM: Structure-activity relationship
(enzyme-inhibiting; selective functionalization of the hydroxyl groups of apoptolidin in order to investigate the enzyme-inhibiting structure-activity relationship)

INDEX TERM: Acetylation
Silylation
(regioselective; selective functionalization of the hydroxyl groups of apoptolidin in order to investigate the enzyme-inhibiting structure-activity relationship)

INDEX TERM: 9000-83-3
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(F0F1; selective functionalization of the hydroxyl groups of apoptolidin in order to investigate the enzyme-inhibiting structure-activity relationship)

INDEX TERM: 476647-30-0, Isoapoptolidin
ROLE: PAC (Pharmacological activity); BIOL (Biological study)
(selective functionalization of the hydroxyl groups of apoptolidin in order to investigate the enzyme-inhibiting structure-activity relationship)

INDEX TERM: 502156-06-1P 502156-07-2P 502156-08-3P 502156-19-6P 502156-20-9P 502156-21-0P 502156-22-1P 502156-23-2P 502156-25-4P
ROLE: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(selective functionalization of the hydroxyl groups of apoptolidin in order to investigate the enzyme-inhibiting structure-activity relationship)

INDEX TERM: 194874-06-1, Apoptolidin
ROLE: RCT (Reactant); RACT (Reactant or reagent)
(selective functionalization of the hydroxyl groups of apoptolidin in order to investigate the enzyme-inhibiting structure-activity relationship)

INDEX TERM: 502156-09-4P 502156-10-7P 502156-11-8P 502156-12-9P 502156-13-0P 502156-14-1P 502156-15-2P 502156-16-3P 502156-17-4P 502156-18-5P 502156-24-3P
ROLE: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(selective functionalization of the hydroxyl groups of apoptolidin in order to investigate the enzyme-inhibiting structure-activity relationship)

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD.

REFERENCE(S):

(1) Anon; Developmental Therapeutics Program NCI/NIH, http://dtp.nci.nih.gov 2002
(2) Chaudhary, K; Abstr Papers Am Chem Soc 2002, V224, PU246
(3) Chen, Y; Abstr Papers Am Chem Soc 2002, V224, PU246
(4) Dulbecco, R; J Exp Med 1957, V106, P167
(5) Hayakawa, Y; J Am Chem Soc 1998, V120, P3524 CAPLUS
(6) Junker, B; Abstr Papers Am Chem Soc 2002, V223, PB236
(7) Kim, J; J Antibiot 1997, V50, P628 CAPLUS
(8) Nicolaou, K; Angew Chem, Int Ed 2001, V40, P3849 CAPLUS
(9) Nicolaou, K; Angew Chem, Int Ed 2001, V40, P3854 CAPLUS
(10) Pennington, J; Org Lett 2002, V4, P3823 CAPLUS
(11) Salomon, A; Chem Biol 2001, V8, P71 CAPLUS
(12) Salomon, A; Org Lett 2001, V3, P57 CAPLUS

(13) Salomon, A; Proc Natl Acad Sci U S A 2000, V97, P14766 CAPLUS
(14) Schuppan, J; Angew Chem, Int Ed 2001, V40, P2063 CAPLUS
(15) Schuppan, J; Tetrahedron Lett 2000, V41, P621 CAPLUS
(16) Sulikowski, G; Org Lett 2000, V2, P1439 CAPLUS
(17) Toshima, K; Tetrahedron Lett 2001, V42, P8873 CAPLUS
(18) Wender, P; Org Lett 2002, V4, P3819 CAPLUS
(19) Xu, J; Abstr Papers Am Chem Soc 2000, V219, P816-ORGN

REFERENCE 3

ACCESSION NUMBER: 138:11196 CA
TITLE: Isoapoptolidin: Structure and Activity of the Ring-Expanded Isomer of Apoptolidin
AUTHOR(S): Wender, Paul A.; Gulledge, Aaron V.; Jankowski, Orion D.; Seto, Haruo
CORPORATE SOURCE: Department of Chemistry, Stanford University, Stanford, CA, 94305-5080, USA
SOURCE: Organic Letters (2002), 4(22), 3819-3822
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 1-6 (Pharmacology)
ABSTRACT:
Apoptolidin (1) is a novel oncolytic lead that induces apoptosis in transformed cell lines with exceptional selectivity. We report the isolation and characterization of a ring-expanded macrolide isomer of apoptolidin: isoapoptolidin (2). The solution conformation of isoapoptolidin is described. The rate of isomerization was measured under biol. relevant conditions and found to approach equilibrium within the time frame of most cell-based assays. Isoapoptolidin's ability to inhibit mitochondrial F0F1-ATPase is over 10-fold less than that of apoptolidin.

SUPPL. TERM: apoptolidin isomer isoapoptolidin isolation characterization ATPase inhibition
INDEX TERM: Conformation
Isomerization
Mitochondria
(structure and activity of isoapoptolidin)
INDEX TERM: 9000-83-3
ROLE: BSU (Biological study, unclassified); BIOL (Biological study)
(F0F1, mitochondrial; structure and activity of isoapoptolidin)
INDEX TERM: 476647-30-0P, Isoapoptolidin
ROLE: PAC (Pharmacological activity); PRP (Properties); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(structure and activity of isoapoptolidin)
INDEX TERM: 194874-06-1, Apoptolidin
ROLE: PAC (Pharmacological activity); BIOL (Biological study)
(structure and activity of ring-expanded isomer of apoptolidin)
REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD.

(1) Anon; http://dtp.nci.nih.gov 2002
(2) Dulbecco, R; J Exp Med 1957, V106, P167
(3) Hayakawa, Y; J Am Chem Soc 1998, V120, P3524 CAPLUS
(4) Humphrey, W; J Mol Graphics 1996, V14, P33 CAPLUS
(5) Kim, J; J Antibiotics 1997, V50, P628 CAPLUS
(6) Mohamadi, F; J Comput Chem 1990, V11, P440 CAPLUS
(7) Nicolaou, K; Angew Chem, Int Ed 2001, V40, P3849 CAPLUS
(8) Nicolaou, K; Angew Chem, Int Ed 2001, V40, P3854 CAPLUS

(9) Nicolaou, K; Chem Commun 2000, P307 CAPLUS
(10) Roberts, H; FEBS Lett 1979, V108, P501 CAPLUS
(11) Salomon, A; Chem Biol 2001, V8, P71 CAPLUS
(12) Salomon, A; Org Lett 2001, V3, P57 CAPLUS
(13) Salomon, A; Proc Natl Acad Sci U S A 2000, V97, P14766 CAPLUS
(14) Schuppan, J; Angew Chem, Int Ed 2001, V40, P2063 CAPLUS
(15) Schuppan, J; Tetrahedron Lett 2000, V41, P621 CAPLUS
(16) Still, W; J Am Chem Soc 1990, V112, P6127 CAPLUS
(17) Sulikowski, G; Abstracts of Papers, 218th National Meeting of the American Chemical Society 1999, 563-ORGN
(18) Sulikowski, G; Org Lett 2000, V2, P1439 CAPLUS
(19) Toshima, K; Tetrahedron Lett 2001, V42, P8873 CAPLUS

REFERENCE 4

ACCESSION NUMBER: 138:2076 CA
TITLE: Toward a stable apoptolidin derivative: identification of isoapoptolidin and selective deglycosylation of apoptolidin
AUTHOR(S): Pennington, James D.; Williams, Howard J.; Salomon, Arthur R.; Sulikowski, Gary A.
CORPORATE SOURCE: Department of Chemistry, Texas A and M University, College Station, TX, 77842, USA
SOURCE: Organic Letters (2002), 4(22), 3823-3825
CODEN: ORLEF7; ISSN: 1523-7060
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
CLASSIFICATION: 10-1 (Microbial, Algal, and Fungal Biochemistry)
ABSTRACT:
Isoapoptolidin was isolated from crude fermentation exts. of the apoptolidin-producing microorganism Nocardiopsis sp. Apoptolidin isomerizes to isoapoptolidin upon treatment with methanolic triethylamine to establish a 1.4:1 equilibrium mixture of isoapoptolidin and apoptolidin. Semisynthesis of a peracetylated and deglycosylated derivative of apoptolidin is also described.

SUPPL. TERM: Nocardiopsis apoptolidin isomer deglycosylation
INDEX TERM: Glycosylation
(deglycosylation; selective deglycosylation of apoptolidin)
INDEX TERM: Nocardiopsis
(identification of isoapoptolidin and selective deglycosylation of apoptolidin)
INDEX TERM: 476647-30-0, Isoapoptolidin
ROLE: NPO (Natural product occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(identification of isoapoptolidin and selective deglycosylation of apoptolidin)
INDEX TERM: 194874-06-1, Apoptolidin
ROLE: PRP (Properties); RCT (Reactant); RACT (Reactant or reagent)
(identification of isoapoptolidin and selective deglycosylation of apoptolidin)
INDEX TERM: 476487-95-3P, Apoptolidin hexaacetate 476487-96-4P
ROLE: PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(identification of isoapoptolidin and selective deglycosylation of apoptolidin)
INDEX TERM: 476487-97-5P
ROLE: SPN (Synthetic preparation); PREP (Preparation)
(identification of isoapoptolidin and selective deglycosylation of apoptolidin)
REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS

RECORD.

(1) Hayakawa, Y; J Am Chem Soc 1998, V120, P3524 CAPLUS
(2) Kim, J; J Antibiot 1997, V50, P628 CAPLUS
(3) Nicolaou, K; Angew Chem, Int Ed 2001, V40, P3849 CAPLUS
(4) Nicolaou, K; Angew Chem, Int Ed 2001, V40, P3854 CAPLUS
(5) Nicolaou, K; J Chem Soc, Chem Commun 2000, P307 CAPLUS
(6) Salomon, A; Chem Biol 2001, V8, P71 CAPLUS
(7) Salomon, A; Org Lett 2001, V3, P57 CAPLUS
(8) Salomon, A; Proc Natl Acad Sci U S A 2000, V97, P14766 CAPLUS
(9) Schuppan, J; Angew Chem, Int Ed 2001, V40, P2063 CAPLUS
(10) Schuppan, J; Tetrahedron Lett 2000, V41, P621 CAPLUS
(11) Sulikowski, G; Org Lett 2000, V2, P1439 CAPLUS
(12) Toshima, K; Tetrahedron Lett 2001, V42, P8873 CAPLUS

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